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CNS Complications of Systemic Malignancy amongst patients attending a Radiotherapy facility in Lagos

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ABSTRACT

Introduction: The Central nervous system (CNS) is a frequent a site of relapse of systemic cancer. There are few data available in literature about the frequency and nature of symptomatic histopathological variants of secondary brain/spinal tumours drawn against the gender/age distribution in our environment. **Objective:** To study the frequency and manifestation of CNS involvement in patients with systemic cancer for a high index of suspicion so that practitioner will have highest index of suspicion to make early diagnosis and treatment in our environment. **Material and methods:** A total of 119 patients with histological confirmed cases of cancer with secondaries to the CNS, were analysed for this study. **Results:** CNS metastasis were more common in female(67%) than male(33%) p = 0.047. Spinal cord metastasis is the most common type of neurological manifestation (66.9%) with p = 0.011. Breast (60.5%) and prostate (21%) were the most common site of primary tumour. Neurological manifestations were mostly associated with advanced Stage tumours (54.9%) (p = 0.000). Approximately half of the cases,56 (54.9%) were presented at late stage (4). Neurological manifestation occurred < 6 months(43.1%)after initial diagnosis of the primary tumour. Spinal/radicular pain was the most prevalent among the patients (43%). CT scan/MRI Imaging in (52.6%) and mode of treatment was radiotherapy (99%) of patients.**Conclusion:** Even though therapy is largely palliative, research should focus on enhancing the efficacy of whole brain radiotherapy and invest in the biosynthesis of synergistic new systemic agents that could also cross the BBB.

Keywords: Malignancy, Metastasis, Neurological manifestation, Brain, Spinal cord blood-brain-barrier

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INTRODUCTION

The Central nervous system (CNS) is a frequent a site of relapse of systemic cancer. The manifestations of CNS metastases are diverse. The deposits may be in the in the brain and or spinal parenchymal with or without associated leptomeningeal deposits. The deposits may be precocious (found before the primary tumour) and synchronous (found within 2 months of the primarytumour) brain metastasis account for approximately 20% of cases; the remaining 80% present with a known primary tumour.[1,2]

Ten to 50% of patients with systemic malignancy develop brain metastases during the course of their disease and metastases account for more than half of all brain tumours in adults.[3] The incidence of CNS metastasis can be as high as 80% as is the case of malignant melanoma, but with common sites being lung 50%, breast 10-15%, melanoma, renal, colorectal, prostate.[4,5] The incidence of brain metastasis is increasing, due to an ever increasing aging population, detection of subclinical disease, therapeutic control of systemic disease and inability of these drugs to penetrate the blood brain barrier, aggressiveness and biology of the tumour.[5,6]

Patients may experience single, few, or several brain metastases. Melanoma and lung cancer are frequently associated with multiple metastases while solitary metastases

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are more commonly seen in patients with breast, colon, and renal-cell carcinoma.[7]

Much needs to be learned about the pathophysiology of CNS metastasis at a molecular level. Investigations of matched primary and metastatic lung tumour specimens in some studies have focused primarily on the mutational status of only EGFR or KRAS. However, available data do not establish any clear correlation between EGFR and KRAS mutation status of primary lung tumours and their propensity to metastasize to the CNS.[8] In Small Cell Lung Carcinoma (SCLC), the most highly aggressive lung cancer subtype with strong predilection for metastasis to the brain, placental growth factor (PLGF) and vascular endothelial growth factor receptor 1 (VEGFR1) expression levels were recently associated with brain metastasis.[8]

Lin and Winer provide an elegant overview of HER-2–positive breast cancer as a paradigm for the problem. The overexpression of HER-2 identifies a more aggressive subtype of breast cancer Patients with TN or HER2-positive tumours showed increased risk for CNS metastases.[5] However, after diagnosis of CNS metastases only surgery and radiotherapy favourably influenced survival.[9]

Tumour's (one or more brain metastases) resectability depends on its location. The majority of brain metastases are located in the cerebral hemispheres (80% to 85%) and up to 15% of metastases develop in the cerebellum.These tumours most often arise in the grey-white junctions, which are near the surface of the brain and hence can be accessed without the need to traverse normal brain. Only 1% to 5% of patients have metastases in the brainstem where surgical access is more limited.[10]

The diagnosis of brain metastasis should be suspected in any cancer patient who develops new neurological symptoms (i.e. presenting with severe headaches, seizures, blurred vision, etc.).[3] Supratentorial metastases may be more easily recognized, but cerebellar metastases can produce subtle early neurologic signs and symptoms that go initially unrecognized such as headache and gait difficulty with or without nausea/vomiting and dizziness.[11]

There are few data available in the literature about the frequency, nature of symptomatic histopathological variants of secondary brain/spinal tumours, gender and age distribution in our environment. We aim to study the frequency and manifestation of CNS involvement in patients with systemic cancer.

MATERIALS AND METHODS

A total of 119 patients with histological confirmed cases of cancer with secondaries to the CNS, from 2003 to 2013 at Eko Hospital radiotherapy Unit were analysed for this study. These patients were referred for radiotherapy treatment during the period of study,the numbers presented per year has been progressively increasing due to awareness and improvement in access to radiodiagnosis facilities such as CT scan, MRI, and Bone scan and enhanced diagnostic imaging has led not only to an increasing incidence of CNS metastases which in turn led to increase in radiotherapy seeking pattern from 2003 till date.

This radiotherapy facility is located at Ikeja, Lagos State, Nigeria. It is one of the three referral centre serving the whole of South Western Region (most populous region) of Nigeria and the only private institution of the three centres. The centre is one of the two radiotherapy institution in Lagos state (the main commercial state of the country), which has the highest population density in Nigeria, of about 15million people.

The records of the patients which contain their background characteristics such as age, sex, clinical, radiologic and pathological variables including histological type, grade and stage were analysed. Pre-treatment and follow up radiological imaging included chest X-ray, X-rays of the bone, bone scan and neuroimaging (cranial magnetic resonance image (MRI) and or computerized tomographic (CT) scan).

The inclusion criteria used in the study were as follows: patients of 18yrs and above, histological confirmation and radiological evidence of disease; exclusion criteria were patients younger than 18years and patients with psychiatric illness.

Descriptive statistics include frequencies (percentage), mean, median, range, and Chi square (or fisher's exact test) as appropriate. The level of significance was fixed at less than 5% probability for chance. All analysis was done using Statistical Package for Social Sciences version 16 statistical software (SPSS, Chicago, IL, USA).

The limitation of this study is that immunohistochemistry was not carried out on most of the patients largely due to lack of infrastructure and financial resource on the part of the patient, who employs the pay-out-of-pocket system to fund their cancer management. The latter is commonplace in this part of the world. Staging not known in 17 patients.

RESULTS

There were 119 patients involved in this study, with majority being females (67%), and a male to female ratio of 1:2.1. The mean and median ages were 44 ± 20.66 and 48 years respectively. Only one of the patients was below 20 years, (50% were between 46-65years, 35% falls within 21-45 years while 17% were above 65 years. 108 (91%) were married, 6% single while 3% were widowed [Table A.1].

Involvement of the Spinal cord with metastasis is the most common type of neurological manifestation (66.9%), 21.2% of the patients had brain metastasis, while 11.9% of the patients had both Spine and Brain metastasis. (p=0.011) [Table A.2].

CNS(spine and brain)metastasis were more common in females (66%) compared with males (33%) p=0.047.

Neurological manifestations were mostly associated with advanced Stage tumours (54.9%), as the stage advanced, the incidence of metastasis increases (p=0.000) [Table A.3].

In most patients, neurological manifestation occur in less than 6 months (43.1%) after initial diagnosis of the primary tumour; the CNS manifestation occurred between 7 to 18 months in 36.2% of the patients; in 11.2% of the patients, the CNS manifestation started within 19 months and 3years after diagnosis, while the least value of manifestation (3.4%) was recorded between 3-5years after the initial diagnosis of the primary tumour.[Table A.4]

Table A.1: Distribution of the demographic profile of patients

Parameter	Number (percentage, %)
Sex	
Male	39 (33)
Female	80 (67)
Age	
<21	1 (7)
21 – 45	41 (35)
46 – 65	57 (50)
>65	20 (17)
Marital status	
Single	7 (6)
Married	108 (91)
Widowed	4 (3)

Table A. 2: Predilection of Breast Cancer to metastasize to the brain or spine

Primary tumour site	Frequency of metastasis involving the CNS (N (%))		Total (%)	P value (Chi square test)
	Brain	Spinal		
Breast	32 (32)	68 (68)	100.00	0.011
Renal	40.00 (40)	60.00 (60)	100.00	

The breast was the most common site of primary tumour (72, 60.5%) followed by prostate (25, 21%) with renal and nasopharynx accounting for 4.2% and 3.4% respectively. Others include Non Hodgkin lymphoma, rectal carcinoma, nasal tumours, osteosarcoma, multiple myeloma and endometrial carcinoma, all of which constitute 7.6% of the total primary sites of tumour. [Table A.5]

Spinal/radicular pain was prevalent among the patients (43.5%), paresis occurs in between 25.1% of the patients while

Table A.3: Distribution of site of Metastases and tumour stage

	Males	Females	Total	p-value
Metastases site				
Brain	4	21	25	0.047
Spine	32	47	79	
Both	3	11	14	
Tumour stage				
II	8	10	18	0.000
III	4	24	28	
IV	12	44	56	

Table A.4: Distribution of neurological manifestations, stage and duration of manifestation

Parameter	Number (%)
Site of cns metastases	
Brain	25 (21.2)
Spine	79 (66.9)
Both	14 (11.9)
Stage at initial diagnosis	
II	18 (17.6)
III	28 (27.5)
IV	56 (54.9)
Duration between initial diagnosis and manifestation of cns metastases	
<6 months	50 (43.1)
7 – 18 months	42 (36.2)
19 months – 3 years	13 (11.2)
3-5 years	4 (3.4)
>5 years	7 (6.0)

Table A.5: Shows distribution of primary site of tumour, histology and grade

Parameter	Number (percentage, %)
Primary site of tumor	
Breast	72 (60.5)
Prostate	25 (21.0)
Renal	5 (4.2)
Nasopharynx	4 (3.4)
Colon	2 (1.7)
Cervix	2 (1.7)
Others	9 (7.6)
Grade	
I	14.3
II	47.6
III	38.1

15.9 % have headache. The neurologic examination reveals hemiparesis/paraparesis in 51% of the patients.[Table A.6]

Over half (52.6%) of the patients were investigated using CT scan/MRI, 28.4% through X-ray, 12.9% through Bone Scan while 6% did both X-ray and CT scan/MRI. Brain metastasis was detected by radiological investigation in 21.1% of the patients and lytic lesion was detected by radiological investigation in the vertebrae of 15.1% the patients. Most of the patients were treated using radiotherapy (99%) while only one patient underwent surgery. [Table A.7]

DISCUSSION & CONCLUSION

Neurological complications of systemic malignance occur frequently in patients with the advent of more effective cancer treatment protocols and prolonging survival of these cancer patients. The incidence of CNS manifestations can be as high as 80% as is the case of malignant melanoma[5,12], and is invariably associated with dismal prognosis manifested by progressive neurological deterioration and a short median survival.[5] In fact, the median survival of untreated patients with metastasis is approximately one month.[13]

When patients with cancer achieved long term remission, significant proportion will experience CNS metastasis as the only site of relapse. This is because there are improved ways of detecting and treating systemic visceral metastatic disease with improved imaging technologies (CT scan, MRI, positron emission tomographic scan, (PET)), genetic profiling of the tumour for appropriate targeting drugs which controls the disease, but most cannot cross the blood brain barrier.[14,15] High tesla MRI can detect lesions as small as 1mm, while PET scan has resulted in early discoveries and remain the standard in brain/spinal cord diagnosis. X-ray, CT scan and MRI were used to diagnose spinal cord compression in our study while CT scan and MRI were used in the diagnosis of brain metastasis. Positron emission tomography is still not available in our country.

Evans et al in their study noted that women with metastatic breast disease under the age of 50 years with oestrogen receptor negative tumour have about 53% risk of developing brain metastasis.[16,17] Though most of them were successfully treated with systemic cytotoxic chemotherapeutic agents, the brain remained a sanctuary for relapse because of the blood brain barrier.[18] Immunohistochemical (IHC) detection has become essential to many malignancies and plays a key role in tumor diagnosis, treatment and prognostic assessment. Identification of HER2 status and administration of target therapy has been found to improve survival as a result of better control of extracranial systemic disease.[5]

Age plays an important role in survival of patients with brain metastasis. The radiation therapy oncology group have devised a recursive partitioning analysis with pre-treatment prognostic characteristic and treatment related variables to decide appropriateness of treatment based on patient's likelihood of survival.[19] They identified three groups of patients according to prognostic factors related to tumour based on karnofsky performance score (KPS), primary tumour status, presence of extracranial metastasis and age. Patients with KPS >70, age <65, no extracranial metastasis and controlled primary tumour are considered class I and have a median survival of 7.1 months, Class II 4.2 months, patients with KPS <70 are class III with a median survival of 2.3 months. A recently published retrospective multi-institutional analysis of 4259 patients with brainmetastases has led to the development of the disease-specific graded prognostic assessment (DS-GPA)

Table A.6: Distribution of clinical features amongst respondents

	Number (%)
Symptoms	
Headache	15.9
Sensory loss	2.42
Seizure activity	4.83
Aphasia	1.45
Speech difficulty	2.42
Visual disturbance	1.45
Nausea/vomiting	2.90
Spinal/radicular pain	43.5
Weakness	25.1
Signs	
Hemiparesis/paraparesis	51.4
Impaired cognition	9.7
Gait disorder	1.1
Hemianopia	0.5
Cerebellar ataxia	0.5
Radiologically viewed mass in the brain	21.1
Radiologically viewed lytic lesion in the vertebrae	15.1
Proptosis	0.5

Table A.7: Shows distribution of investigation, treatment and follow-up among respondents

Parameter	Number (%)
Investigation	
X –ray	33 (28.4)
CT scan/MRI	61 (52.6)
Bone Scan	15 (12.9)
X-ray+CT scan/MRI	7 (6.0)
Treatment	
Radiotherapy	116 (99.1)
Surgery	1 (0.9)
Follow up	
Dead	4 (3.4)
On treatment	9 (7.6)
Defaulted	32 (27.1)
Discharged/referred	73 (61.9)

scale that may provide a more accurate estimate of the prognosis. In addition to age, KPS, extracranial disease and number of metastases, prognosis also depends on the primary tumour type.[20]

In our study, 50% were between 46-65years, 35% fell within 21-45 years, 17% were above 65 years and one (0.8%) respondent was below 20years of age.

Central nervous system metastases are a common feature of women's metastatic illness, and are present at autopsy in 30% of women diagnosed with breast cancer.[21] Involvement of the spinal cord (66.9%) with metastasis is the most common type of malignancy. In our series, we found out that close to a quarter (21.2%) of the patients have brain metastases while 11.9% of the patients have both spine and brain metastasis. Malignant spinal compression is a common neurological complication of advanced malignancy. Metastases to the spinal cord column occur in 3-5% of all patients with cancer. Most commonly those with breast cancer, prostate and lung cancer in whom the incidence may be as high as 19%. A population based study in Canada estimated that at least 2.5% of all people with cancer experienced one or more episodes of spinal cord compression in the five years preceding death.[22]

Some primary tumours are much more likely to metastasise to the CNS e.g. small cell lung carcinoma. Such is the predisposition for brain metastasis that patients are often treated with prophylactic cranial irradiation.[23] Triple negative breast cancer have higher tendency to metastasise to the brain resulting in poor prognosis.[24,25] However, tumours with a high incidence in the general population are the most commonly encountered brain metastasis; Lung and breast account for approximately two thirds.[26]The result from our study shows that breast cancer has the highest incidence of CNS metastasis with 60.5% followed by prostate with 21%.

In our study, a greater percentage (54.9%) of patients that developed CNS/leptomeningeal complications were those patients with visceral manifestations (stage 4) followed by stage III 27.5% while patients with stage II later developed brain metastasis. In most of the patients, neurological manifestations occur in less than 6 months (43.1%) after presentation, 7 to 18 months in 36.2%, 11.2% between 19 months and 36 months while 3.4% present with CNS manifestation after 5 years.

Brain metastases cause symptoms by at least two mechanisms: they can directly damage nerve tissue, provoking focal symptoms such as hemiparesis, aphasia or ataxia, or they can raise intracranial pressure which causes diffuse symptoms. Headaches, nausea and vomiting suggest increased intracranial pressure. In our study, the symptoms presented in patients with brain metastasis included headaches 15.9%, seizures 4.83%, aphasia and speech disturbances 3.87%, visual disturbance 1.45%, Nausea and vomiting 2.9%, impaired cognition 9.7%, hemianopia 0.5%, cerebellar ataxia 0.5%.

While most cancers cause spinal cord compression by direct extension from a metastasis in the vertebrae body in 75% of cases, soft tissue epidural metastasis are found in the remaining 25%, frank bone collapse may occur with bone fragment sometime adding to the compression. Blockages of venous outflow or central perforating vessels in the cord result in ischaemia and vasogenic cord oedema. Prostaglandin E2 (PGE2) and in response to hypoxia, vascular endothelial growth factor (VEGF) increase vascular permeability, which leads to vasogenic oedema. Neurologic dysfunction from an ischaemic cord arises from demyelination mediated by lipid peroxidation and both enzymatic and nonenzymatic lipid hydrolysis. The spinal cord may also infarct from ischaemia due to blockage of venous flow, occlusion of small arteries or occlusion of the major arteries. Metastatic spinal cord compression (MSCC) usually present with a history of back pain, sensory loss, paralysis and loss of sphincter control.[27] In our study, patients with spinal cord compression presented with spinal/radicular pain (43.5%), hemiparesis/paraparesis (51.4%), sensory loss (2.42%), and in both brain and spinal cord metastasis, general weakness accounted for 25.1%.

The management of patients with cerebral metastasis involves a multidisciplinary team with contribution from the neurosurgeons, medical/radiation oncologist, palliative care physicians, specialists' nurses and neuro-radiologist. Treatment should be individualized for patients based on their presentation taking into consideration clinical disease status which should be discussed by multidisciplinary team. The treatment choices are limited; only patients with single brain metastasis benefit from surgery or radiosurgery if lesions are <3cm; while whole brain radiotherapy, corticosteroids, anticonvulsant and supportive care remain the standard treatment for multiple brain metastasis. The goal of therapy in malignant spinal cord compression is palliative and is aimed at relieving the pain, decompressing the spinal cord by debulking the tumour, and maintaining ambulation.[27]

In conclusion, even though breast cancer remains the most common cause of CNS complications of distant metastasis in our environment, the goal of therapy by and large at this stage would be majorly palliative. Cancers with metastasis in the CNS can result in aggravating and more distressing signs and symptoms if left untreated, but prompt and early diagnosis followed by treatment due to knowledge of its

presentation and treatment modality by the physician can improve patient quality of life tremendously. Though their treatment continue to evolve, research should focus on enhancing the efficacy whole brain radiotherapy which is a main traditional therapy, with the aim of increasing the time to neurological failure as well as promising new systemic agents that synergise with radiation by potentially crossing the blood brain barrier.

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PA – conceived the original idea, designed the study, made the first draft of the manuscript; **IA –** data collection, arrangement and manuscript review; **IO, DK and KK –** manuscript review, conceptual contributions.

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